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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/142,613	04/19/1999	KOICHI ISHIGURO	1416/OP551PC	2418

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EXAMINER
GUCKER, STEPHEN

ART UNIT	PAPER NUMBER
1647	30

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/142,613	Ishiguro et al.
Examiner	**Group Art Unit**
Stephen Gucker	1647

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☑ Responsive to communication(s) filed on 3/6/03.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☑ Claim(s) 1 + 6 - 24 is/are pending in the application.

Of the above claim(s) 1, 6, 8, + 10 - 23 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 7, 9, + 24 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☑ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

Part III DETAILED ACTION

1. Applicant's election with traverse of Group III, claims 7, 9, and 24 in Paper No. 29 is acknowledged. The traversal is on the ground(s) that a search on Groups I and II has already been conducted and a restriction at this point is contrary to the policy of compact prosecution. This is not persuasive due to the plethora of previous 112, 2nd paragraph rejections noted by the previous Examiner in Paper No. 17, filed 5/9/01, on pages 2-3. In addition, this argument is not persuasive because the enablement issues surrounding the method of Alzheimer's Disease diagnosis, an art-recognized difficult clinical diagnosis to make with no routine biochemical or immunological testing procedure available even at the present time, let alone at Applicant's effective filing date, places an undue burden on the Examiner. Because the searches for prior art concerning just the antibodies themselves without any intended use in a diagnostic process are not co-extensive with searches concerning the enablement of the claimed method, and different issues would have to be considered, a search burden exists and restriction is proper.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1, 6, 8, and 10-23 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 29.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Any objections or rejections made in a previous Office Action that are not herein reinstated have been withdrawn.

5. Claims 7, 9, and 24 are objected to as being ultimately dependent upon non-elected base claims.

Appropriate correction is required.

6. The disclosure is objected to because of the following informalities: the amendment filed 2/26/01, Paper No. 15, Amendment C, in the Brief Description of the Drawings section, leaves blank the number of the "Example" described in Figures 2-4 and Figure 6.

Appropriate correction is required.

7. Claims 7, 9, and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting Alzheimer's disease (AD) in either brain samples or cerebrospinal fluid (CSF), does not reasonably provide enablement for detecting Alzheimer's disease in the broader genus of body fluid samples. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specification teaches that the hyperphosphorylated tau protein that is of diagnostic importance to the instant invention is produced from neurofibrillary degeneration in the brain (page 2, lines 10 to page 3, line 6). The instant working examples demonstrate that this hyperphosphorylated tau protein can be detected with antibodies in both the brain and the CSF. However, the specification does not adequately describe or provide guidance for, nor are there any working examples, of

diagnostic AD hyperphosphorylated tau protein present in blood, saliva, urine, lymph, sweat, semen, tears, or any other species of the genus of body fluid sample. While it is reasonable to expect that the degenerating neurons of the AD brain would break down and release diagnostic hyperphosphorylated tau protein from the brain and into the CSF, it is not reasonable to predict that said hyperphosphorylated tau protein would escape from this closed system because of the tight cellular junctions formed by specialized epithelial cells that compose the brain-blood barrier and shield the brain from large molecules floating freely in the general circulation, and also prevent the free escape of brain constituents into the general circulation. The specification as written does not place a method for diagnosing AD from the genus of body fluid samples into the hands of the skilled artisan with a reasonable expectation of success without forcing undue experimentation to be performed for this reason.

8. Claims 7, 9, and 24 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. The claims fail to clearly enumerate the steps of the method being performed so as to make clear the metes and bounds of the invention. "To detect from the reactivity of said antibodies whether said individual has Alzheimer [sic]" does not set forth clearly such steps as:

a) obtaining a brain or CSF sample from an individual suspected of having Alzheimer's disease;

b) reacting said sample with an antibody that was raised against an immunogen consisting of SEQ ID NO:2 or consisting of SEQ ID NO:2 with a reactive functional group at the amino or carboxyl terminus of SEQ ID NO:2 which is bound to a carrier protein as a hapten;

c) allowing specific binding of said antibody to occur to said sample under appropriate incubation conditions; and

d) detecting the reaction of said specific binding of said antibody with said sample as detecting that said individual has Alzheimer's disease.

9. The declaration filed 11/15/02 under 37 CFR 1.132 by Ishiguro is persuasive in showing that prior art monoclonal antibody AT8 does not specifically bind to SEQ ID NO:2 as does the antibody of the instant invention raised against SEQ ID NO:2. Therefore, a product-by-process limitation that includes the use of an antibody raised against a polypeptide consisting of SEQ ID NO:2 is free of the previous art of record. However, Applicant is cautioned against using any open language in regards to the instant invention because SEQ ID NO:2 is a fragment found in hyperphosphorylated tau protein, and the use of the word "comprises" anywhere in the claim reciting SEQ ID NO:2 opens the claim up to encompass the previous art of record which uses antibodies, including AT8, which was raised against a polypeptide "comprising" SEQ ID NO:2, AT8 will bind to a polypeptide "comprising" SEQ ID NO:2, even though AT8 does not specifically bind to a polypeptide "consisting of" SEQ ID NO:2 as aptly demonstrated by the instant declaration.

10. Claims 7, 9, and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Vandermeeren et al. ("Vandermeeren") for reasons of record and the open language of the claims as set forth above.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 7, 9, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sato et al. ("Sato", Peptide Chemistry 1994) in view of Ishiguro et al. ("Ishiguro", Neurosci Lett. 202, 1995). Sato discloses that paired helical filaments (PHFs) accumulate in the neuron of AD brain and highly phosphorylated tau protein was found to be a component of PHFs. Also, Sato discloses instant SEQ ID NO:2 as a phosphorylated fragment of tau protein and suggests making antibodies against SEQ ID NO:2 (pages 109 and 112). Sato does not disclose that antibodies

raised against SEQ ID NO:2 would not bind to non-phosphorylated SEQ ID NO:2. Ishiguro discloses antibodies against instant SEQ ID NO:2 that do not react to non-phosphorylated SEQ ID NO:2 (Figures 1-3). Ishiguro also teaches that PHFs are a hallmark of AD and that PHFs contain highly phosphorylated tau protein (page 81). It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the antibodies suggested or made in the references to diagnose AD because both references teach that highly phosphorylated tau protein occurs in AD and antibodies that bind specifically to phosphorylated tau protein fragments but do not bind to non-phosphorylated tau protein fragments (as in the Ishiguro reference) would be *prima facie* obvious to use for the diagnosis of AD because a hallmark of AD is that PHFs contain highly phosphorylated tau protein.

13. It is noted by the Examiner that either the Sato or the Ishiguro references listed above would be held as prior art against any of the claims drawn to the antibody product produced by using SEQ ID NO:2 as an immunogen.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Gucker whose telephone number is (703) 308-6571. The examiner can normally be reached on Monday to Friday from 0930 to 1800. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623. The fax phone number for this Group is currently (703) 308-4242, but Applicant should confirm this by phoning the Examiner before faxing.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SG

Stephen Gucker

June 30, 2003

Gary L. Kunz

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1